PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer: protocol for a network meta-analysis of randomized controlled trials
AUTHORS	Hu, Qiancheng; Wang, Xin; Chen, Ye; Li, Xiaofen; Luo, Ting; Cao, Dan

VERSION 1 – REVIEW

REVIEWER	Dr Caroline S Clarke University College London (UCL)
REVIEW RETURNED	02-Apr-2020

GENERAL COMMENTS	Thanks very much for the opportunity to review this very important and interesting paper. I have made a few comments below, and hope that they are helpful to the authors. I am a health economist, specialising in economic evaluation alongside clinical trials in a number of different disease areas, and published a paper a while ago on a 3-arm cost-effectiveness analysis looking at different durations of trastuzumab in early breast cancer, based on in an initial network meta-analysis. General comments: What will this study add in top of the various systematic reviews that have already been done and that you discuss? Why is a NMA better than a systematic review? What gaps in knowledge in this area will your study fill? I agree that it is worth doing, but perhaps spell this out more explicitly. There were a lot of language issues and typos. I have mentioned some of them here, but there are more. Typos: please change “ClinicalTrils.gov” to “ClinicalTrials.gov” (p6, p11) Ethics and dissemination (p7, and p19-20) Will the findings from the study also be helpful to policy makers? Clinicians cannot always change practice alone. For the dissemination, will the authors also engage patients and the public? They have a very strong influence in this area. If the patients are not on board with reductions in duration then it is very unlikely that reductions will become acceptable. Strengths (p7), “Our purpose of this NMA is to synthesize all available evidence…”: Will you really be able to synthesise “all” available evidence? My understanding of NMA is that, similarly to the systematic reviews,

	you can (should) only synthesis data together that come from jointly randomisable trials (Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Research Synthesis Methods. 2012; 3: p. 80±97. doi: 10.1002/jrsm.1037 PMID: 26062083). I hope you will be able to identify all available evidence, but it might not all be synthesisable in a meaningful way. Strengths (p7), "…identify the duration of trastuzumab treatments with the greatest value in HER2 positive early breast cancers." What do you mean here by "value"? Perhaps clarify this here. Strengths (p7), "We will plan subgroup and sensitivity analyses to assess the robustness and reliability of findings in our NMA" When will this be planned? I think you have already planned subgroup analysis according to ER status and node status (positive or negative in each case). Limitations (p8): I suspect you might also find that lack of clarity and detail in reporting will be a big challenge. Also, there are likely to be several studies that are mentioned at conferences and then the full paper is not published. Introduction (p9), syntax: "At present, a 1-year of trastuzumab for targeted therapy…" Please remove the extraneous "a" before "1-year". Please also remove the hyphen in "1-year". Introduction (p10), syntax: "As mentioned above, there was a little direct comparison among…" Please remove the extraneous "a" before "little". Introduction (p10), syntax: "…in part to half of RCTs including N9831, NSABP-B31, BCIRG 006 and FinHER trials compared active therapy to inactive interventions (e.g., placebo)" Please change "compared" to "comparing". Introduction (p10), clarity: "…and addressed that 12 months of trastuzumab was still considered the optimal treatment for early HER2-positive breast cancer, with a significant increase in cardiac events". Please re-word this to clarify the meaning: "…and suggested that 12 months of trastuzumab was still considered the optimal treatment for early HER2-positive breast cancer, albeit with a significant increase in cardiac events". You could also perhaps mention here that 12 months was not universally better for all patients. This presumably is why you are looking at subgroups of ER-positive/negative and node-positive/negative disease – you could comment further on this? Introduction (p10), reference: "Network meta-analysis (NMA) has indirectly evaluated relative efficacy and toxicity of multiple durations of adjuvant trastuzumab therapies in HER2-positive early breast cancer". Please give a reference for this statement, e.g. Clarke CS, Hunter RM, Shemilt I, Serra-Sastre V; Multi-arm Cost-Effectiveness Analysis (CEA) comparing different durations of adjuvant trastuzumab in early breast cancer, from the English NHS payer

	perspective. PLOS ONE (2017)), 12(3): e0172731. doi: 10.1371/journal.pone.0172731. Search Strategy (p11), clarity: “Additional RCTs related to the topic will be included after their publication” What do you mean by this? You say in the previous sentence you are including work published until 16 June 2019. Please check and streamline. Search Strategy (p11), clarity: “Two reviewers who have been trained in data extraction will independently conduct search strategies” But they will use the same strategy, correct? Please clarify this, as at the moment it suggests they will conduct searches using different strategies. Please note that one conducts a search, using a search strategy, but one does not conduct a search strategy. Search Strategy (p11), clarity: “…from eligible reviews and relevant trials to identify additional potential studies” Please change “studies” at the end of the sentence to “papers” or “reports”. Typo, p12: please change PRIMSA to PRISMA. Search Strategy (p12), clarity: “MeSH and Subheadings were combined with ‘AND’ or ‘OR’” Please change “were” to “will be”. Search Strategy (p12), typo: “Two independent reviewers will screen the titles/abstracts of related studies based on an inclusion and exclusion criteria” Please remove “an”. Please note that “criteria” is plural. Eligibility criteria (p12), clarity: “Populations: HER2-positive early breast cancer of any age or nationality” Please add “patients with”, so that it reads: “Populations: patients with HER2-positive early breast cancer of any age or nationality”, otherwise you are suggesting that the cancers have a nationality, which doesn’t make sense. Eligibility criteria (p12-13), clarity: “We are also interested in the impact of placebo/observation as adjuvant treatment” What does this mean here? Please clarify. Eligibility criteria (p13), clarity: “Comparators: all eligible interventions with one another” Please clarify the wording here. It seems that you are possibly mixing up “comparisons” and “comparators” in the same breath. Eligibility criteria (p13), contradiction: “We will include studies published in English without date limited” Elsewhere you say that the date range is “from inception to June 16, 2019” Please streamline and clarify this. Eligibility criteria (p13), syntax: “Studies not meet the inclusion criteria will be excluded” Please change “meet” to “meeting”.

	Eligibility criteria (p13), clarity: “Retrospective and prospective cohort studies” Do you mean that you are excluding non-randomised studies? If so, perhaps state this more explicitly. Outcomes (p13), comment: “…acceptability (defined as the proportion of patients who discontinued trastuzumab)” You might find that this is not well reported. What will you do if this is the case? Data extraction and management (p14), syntax: “If duplicate publications are identified, the update data will be included” Please change “update” to “most recent” or “most up-to-date”. Bias risk (p14), comment: You have left out “blinding of outcome assessment (detection bias). Was this deliberate? Perhaps discuss/justify this. Bias risk (p14), typo: Please change “selective outcome reporting” to “selective reporting”. It is the reporting as a whole which is important here, but just reporting of the specific primary or secondary outcomes of a trial. Quality of evidence (p15), typos: Line 12: please change “study” to “studies” Line 22: please change “categorizes” to “categories” Line 30: please change “evidences” to “evidence” Quality of evidence (p15), reference: Please add the reference for CINeMA: “Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the quality of evidence from a network meta-analysis. PloS One. 2014;9(7):e99682” Statistical analysis (p15), clarity: “Results regarding the OS and DFS are calculated HR with 95% confidence intervals CI” Please fix the language here. Statistical analysis (p15), clarity: “The results of probability statements of intervention effects will be ranked” What does this mean? Please explain and clarify. Statistical analysis (p16), clarity: “The interventions with surface under the cumulative ranking (SUCRA) of being the most effective in term of efficacy and safety will be evaluated to interpretation of relative effect of comparisons” This does not make any sense as it stands, please re-word. E.g. something like: “The interventions will be ranked by surface under the cumulative ranking curve, for each outcome measure…” Statistical analysis (p16), clarity: “The benefit-risk analysis of efficacy and toxicity within each comparison will also be completed” Which comparisons? Please explain and clarify here.

	Statistical analysis (p16), typos: Please check the wording/spelling for “fixed effects models” and “random effects models”. Subgroup analysis (p16), syntax: “We will explore whether a particular subtypes of breast cancer” Please remove the extraneous “a” before “particular”. Subgroup analysis (p17), comment: “The subgroup analyses will be conducted regardless of heterogeneity estimates” Why? Please justify this. Sensitivity analysis (p17), typo: “observe the impact of the number of positive lymph node” Please change “node” to “nodes”. Discussion (p17), clarity: “Despite highly effective in treatment with trastuzumab for HER2-positive early breast cancer, substantial socio-economic burden…” Please clarify this, e.g. “Despite trastuzumab being highly effective in treatment for HER2-positive early breast cancer, its substantial socio-economic burden…”. Discussion (p17), clarity: “deemed that 83% four-year DFS with six months trastuzumab is acceptable” Please explicitly state what this is compared to, and mention that this is a trade off against cardiotoxicity. Please also change “is” to “would be”, because this was a thought experiment asking clinicians what they thought would be acceptable. Discussion (p17), clarity: “The trade-offs between efficacy and cardiotoxicity were considerable” What does “were considerable” mean here? Please clarify what this sentence is trying to say. Discussion (p17), comment: “This benefit-risk analysis is important information to help clinicians and patients choose optimum duration” And policy makers? See my earlier comment. Discussion (p18), syntax: “…for de-escalating duration treatment, without compromise of their efficacy” Please change to “…for de-escalating duration of treatment, without compromising efficacy” Discussion (p18), syntax: “…that de-escalating chemotherapy was candidate for older and stages I HER2-positive breast cancer” Please fix the wording, e.g.: “…that de-escalating chemotherapy was a good candidate for older patients and those with stage I HER2-positive breast cancer” Discussion (p18), typo: “…another option of for patients with…” Please remove “of”.

	Discussion (p18), typos: "…the results of system review will fill a pivital…" Please change to "…the results of our systematic review will fill a pivotal…" Page 20: "Patient and public involvement No patient involvement" I advise that you have some patient input – see my earlier comment.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Thanks for your valuable review comments. Our team learns more about network meta-analysis. We believe that we have many more opportunities to invite you to review our manuscript in the future. Please see detailed feedback to your comments as following:

General comments:

What will this study add in top of the various systematic reviews that have already been done and that you discuss? Why is a NMA better than a systematic review? What gaps in knowledge in this area will your study fill? I agree that it is worth doing, but perhaps spell this out more explicitly.

Answer: Pivotal pairwise meta-analyses evaluated the direct efficacy and toxicity between shorter durations of trastuzumab and standard option, but these pairwise meta-analyses could not evaluate shorter durations of trastuzumab (6 months, 12 weeks, or 9-weeks durations of trastuzumab) in terms of efficacy and safety in a single analysis. High-quality randomised controlled trials (RCTs) confirmed that multiple treatment durations of trastuzumab were effective treatments for HER2-positive early breast cancers, but not all head-to-head trials were performed to evaluate relative efficacy and safety. NMA has indirectly evaluated relative efficacy and toxicity of multiple durations of adjuvant trastuzumab therapies in HER2-positive early breast cancer. To address the aforementioned debate and determine the most appropriate treatment options, we will conduct NMA to integrate existing evidence available, based on direct and indirect comparisons of efficacy and safety, and to determine the duration of trastuzumab treatments (24 months vs 12 months vs 6 months vs 12weeks vs 9 weeks vs placebo/observation/zero) with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.

There were a lot of language issues and typos. I have mentioned some of them here, but there are more.

Typos: please change "ClinicalTrils.gov" to "ClinicalTrials.gov" (p6, p11)

Answer: Yes, we have done it.

Ethics and dissemination (p7, and p19-20)

Will the findings from the study also be helpful to policy makers? Clinicians cannot always change practice alone. For the dissemination, will the authors also engage patients and the public? They have a very strong influence in this area. If the patients are not on board with reductions in duration then it is very unlikely that reductions will become acceptable.

Answer: Yes, we have changed it.

Strengths (p7), "Our purpose of this NMA is to synthesize all available evidence…":

Will you really be able to synthesise "all" available evidence? My understanding of NMA is that, similarly to the systematic reviews, you can (should) only synthesis data together that come from jointly randomisable trials (Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis tool. Research Synthesis Methods. 2012; 3: p. 80±97. doi: 10.1002/jrsm.1037 PMID: 26062083). I hope you will be able to identify all available evidence, but it might not all be synthesisable in a meaningful way.

Answer: Yes, we have changed it. To address the aforementioned debate and determine the most appropriate treatment options, we will conduct NMA to integrate existing evidence available, based on direct and indirect comparisons of efficacy and safety, and to determine the duration of trastuzumab treatments (24 months vs 12 months vs 6 months vs 12weeks vs 9 weeks vs placebo/observation/zero) with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.

Strengths (p7), "…identify the duration of trastuzumab treatments with the greatest value in HER2 positive early breast cancers."
What do you mean here by "value"? Perhaps clarify this here.
Answer: Answer: Yes, we have changed it. To address the aforementioned debate and determine the most appropriate treatment options, we will conduct NMA to integrate existing evidence available, based on direct and indirect comparisons of efficacy and safety, and to determine the duration of trastuzumab treatments (24 months vs 12 months vs 6 months vs 12weeks vs 9 weeks vs placebo/observation/zero) with the greatest impact on therapeutic outcomes in HER2 positive early breast cancers.

Strengths (p7), "We will plan subgroup and sensitivity analyses to assess the robustness and reliability of findings in our NMA"
When will this be planned? I think you have already planned subgroup analysis according to ER status and node status (positive or negative in each case).
Answer: Yes, we have changed it. We will perform subgroup and sensitivity analyses to assess the robustness and reliability of findings in our NMA.
Limitations (p8): I suspect you might also find that lack of clarity and detail in reporting will be a big challenge. Also, there are likely to be several studies that are mentioned at conferences and then the full paper is not published.
Answer: Yes, you are right. The lack of clarity and detail in reporting is a big challenge in network and pair-wise meta-analyses, we will attempt to contact study authors and relevant pharmaceutical companies if important data are not reported.
Introduction (p9), syntax: "At present, a 1-year of trastuzumab for targeted therapy…"
Please remove the extraneous "a" before "1-year". Please also remove the hyphen in "1-year".
Answer: Yes, we have done it.
Introduction (p10), syntax: "As mentioned above, there was a little direct comparison among…"
Please remove the extraneous "a" before "little".
Answer: Yes, we have done it.
Introduction (p10), syntax: "…in part to half of RCTs including N9831, NSABP-B31, BCIRG 006 and FinHER trials compared active therapy to inactive interventions (e.g., placebo)"
Please change "compared" to "comparing".
Answer: Yes, we have done it.

Introduction (p10), clarity: "…and addressed that 12 months of trastuzumab was still considered the optimal treatment for early HER2-positive breast cancer, with a significant increase in cardiac events".
Please re-word this to clarify the meaning: "…and suggested that 12 months of trastuzumab was still considered the optimal treatment for early HER2-positive breast cancer, albeit with a significant increase in cardiac events".
You could also perhaps mention here that 12 months was not universally better for all patients. This presumably is why you are looking at subgroups of ER-positive/negative and node-positive/negative disease – you could comment further on this?
Answer: Yes, we have done it.

Introduction (p10), reference: “Network meta-analysis (NMA) has indirectly evaluated relative efficacy and toxicity of multiple durations of adjuvant trastuzumab therapies in HER2-positive early breast cancer”.
Please give a reference for this statement, e.g. Clarke CS, Hunter RM, Shemilt I, Serra-Sastre V; Multi-arm Cost-Effectiveness Analysis (CEA) comparing different durations of adjuvant trastuzumab in early breast cancer, from the English NHS payer perspective. PLOS ONE (2017)), 12(3): e0172731.doi: 10.1371/journal.pone.0172731.
Answer: Yes, we have done it.

Search Strategy (p11), clarity: “Additional RCTs related to the topic will be included after their publication”
What do you mean by this? You say in the previous sentence you are including work published until 16 June 2019. Please check and streamline.
Answer: Yes, we deleted the sentence “Additional RCTs related to the topic will be included after their publication”.

Search Strategy (p11), clarity: “Two reviewers who have been trained in data extraction will independently conduct search strategies”
But they will use the same strategy, correct? Please clarify this, as at the moment it suggests they will conduct searches using different strategies. Please note that one conducts a search, using a search strategy, but one does not conduct a search strategy.
Answer: Yes, we think using different strategies is a good and new method, but two reviewers use the same strategy in order to fully search potentially eligible studies. Also this is a common practice in network meta-analysis and pairwise meta-analysis, such that it could be repeated (1).
1. Mahasha PW, Ndwandwe DE, Mavundza EJ, et al. Systematic review protocol on Bacillus Calmette-Guerin (BCG) revaccination and protection against tuberculosis. BMJ Open 2019;9:e027033.

Search Strategy (p11), clarity: “…from eligible reviews and relevant trials to identify additional potential studies”
Please change “studies” at the end of the sentence to “papers” or “reports”.
Answer: yes, we have changed it.
Typo, p12: please change PRIMSA to PRISMA.
Answer: yes, we have changed it.
Search Strategy (p12), clarity:
“MeSH and Subheadings were combined with ‘AND’ or ‘OR’”
Please change “were” to “will be”.
Answer: yes, we have changed it.
Search Strategy (p12), typo:
“Two independent reviewers will screen the titles/abstracts of related studies based on an inclusion and exclusion criteria”
Please remove “an”. Please note that “criteria” is plural.
Answer: yes, we have changed it.
Eligibility criteria (p12), clarity:
“Populations: HER2-positive early breast cancer of any age or nationality”
Please add “patients with”, so that it reads: “Populations: patients with HER2-positive early breast cancer of any age or nationality”, otherwise you are suggesting that the cancers have a nationality, which doesn’t make sense.
Answer: yes, we have changed it.
Eligibility criteria (p12-13), clarity:
“We are also interested in the impact of placebo/observation as adjuvant treatment”
What does this mean here? Please clarify.

Answer: Placebo/observation/zero as adjuvant treatment was an early research method, such as BCIRG 006. To fully compare the optimum duration of adjuvant trastuzumab in treatment of human epidermal growth factor receptor-2 positive early breast cancer, Placebo/observation could be used as a bridge for indirect analysis. Thus, we are also interested in the impact of placebo/observation/zero as adjuvant treatment.
Eligibility criteria (p13), clarity:
"Comparators: all eligible interventions with one another"
Please clarify the wording here. It seems that you are possibly mixing up "comparisons" and "comparators" in the same breath.
Answer: we revised that one year 12 months of trastuzumab treatment compared with placebo/observation/zero, or other durations of adjuvant trastuzumab.
Eligibility criteria (p13), contradiction:
"We will include studies published in English without date limited"
Elsewhere you say that the date range is "from inception to June 16, 2019"
Please streamline and clarify this.
Answer: we have revised it. We will include studies published in English regardless of publication status.
Eligibility criteria (p13), syntax:
"Studies not meet the inclusion criteria will be excluded"
Please change "meet" to "meeting".
Answer: yes, we have changed it.
Eligibility criteria (p13), clarity:
"Retrospective and prospective cohort studies"
Do you mean that you are excluding non-randomised studies? If so, perhaps state this more explicitly.
Answer: Yes, we include RCTs, and excluded non-randomised studies, such as prospective cohort studies.
Outcomes (p13), comment:
"…acceptability (defined as the proportion of patients who discontinued trastuzumab)"
You might find that this is not well reported. What will you do if this is the case?
Answer: Most papers reported the completion rate, so we will calculate the unfinished rate by 1-completion rate in each group.
Data extraction and management (p14), syntax:
"If duplicate publications are identified, the update data will be included"
Please change "update" to "most recent" or "most up-to-date".
Answer: yes, we have changed it.
Bias risk (p14), comment:
You have left out "blinding of outcome assessment (detection bias). Was this deliberate? Perhaps discuss/justify this.
Answer: we have added "blinding of outcome assessment".
Bias risk (p14), typo:
Please change "selective outcome reporting" to "selective reporting". It is the reporting as a whole which is important here, but just reporting of the specific primary or secondary outcomes of a trial.
Answer: yes, we have changed it.

Quality of evidence (p15), typos:
Line 12: please change "study" to "studies"
Line 22: please change "categorizes" to "categories"
Line 30: please change "evidences" to "evidence"
Answer: yes, we have changed it.

Quality of evidence (p15), reference:

Please add the reference for CINeMA: “Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. Evaluating the quality of evidence from a network meta-analysis. PloS One. 2014;9(7):e99682”
Answer: yes, we have added it.

Statistical analysis (p15), clarity:
“Results regarding the OS and DFS are calculated HR with 95% confidence intervals CI”
Please fix the language here.
Answer: yes, we have changed it. Pooled hazard ratios (HRs) for OS and DFS with 95% confidence intervals (CIs) will be calculated using both random effect and fixed effect model.
Statistical analysis (p15), clarity:
“The results of probability statements of intervention effects will be ranked”
What does this mean? Please explain and clarify.
Answer: yes, we have changed it. The results of comparative effectiveness and safety probability statements of intervention effects will be ranked; and rank plots across all outcomes will be generated.
Statistical analysis (p16), clarity:
“The interventions with surface under the cumulative ranking (SUCRA) of being the most effective in term of efficacy and safety will be evaluated to interpretation of relative effect of comparisons”
This does not make any sense as it stands, please re-word. E.g. something like: “The interventions will be ranked by surface under the cumulative ranking curve, for each outcome measure…”
Answer: yes, we have changed it. The interventions with surface under the cumulative ranking (SUCRA) in term of efficacy and safety will be evaluated to interpret relative effect of comparisons.
Statistical analysis (p16), clarity:
“The benefit-risk analysis of efficacy and toxicity within each comparison will also be completed”
Which comparisons? Please explain and clarify here.
Answer: Yes, we have changed it. We will seek to compare the risk-benefit profile of all comparators in terms of efficacy and toxicity.
Statistical analysis (p16), typos:
Please check the wording/spelling for “fixed effects models” and “random effects models”.
Answer: Yes, we have changed it. Pooled hazard ratios (HRs) for OS and DFS with 95% confidence intervals (CIs) will be calculated using both fixed- and random-effects model.
Subgroup analysis (p16), syntax:
“We will explore whether a particular subtypes of breast cancer”
Please remove the extraneous “a” before “particular”.
Answer: Yes, we have changed it.
Subgroup analysis (p17), comment:
“The subgroup analyses will be conducted regardless of heterogeneity estimates”
Why? Please justify this.
Answer: Yes, we deleted it.
Sensitivity analysis (p17), typo:
“observe the impact of the number of positive lymph node”
Please change “node” to “nodes”.
Answer: Yes, we have done it.
Discussion (p17), clarity:
“Despite highly effective in treatment with trastuzumab for HER2-positive early breast cancer, substantial socio-economic burden…”
Please clarify this, e.g. “Despite trastuzumab being highly effective in treatment for HER2-positive early breast cancer, its substantial socio-economic burden…”.
Answer: Yes, we have done it.
Discussion (p17), clarity:
“deemed that 83% four-year DFS with six months trastuzumab is acceptable”

Please explicitly state what this is compared to, and mention that this is a trade off against cardiotoxicity. Please also change “is” to “would be”, because this was a thought experiment asking clinicians what they thought would be acceptable.
Answer: Yes, we have changed it. Compared to the 12-month durations of trastuzumab treatments, most clinicians suggested that a drop to 83% four-year DFS with six months trastuzumab would be also acceptable.
Discussion (p17), clarity:
“The trade-offs between efficacy and cardiotoxicity were considerable”
What does “were considerable” mean here? Please clarify what this sentence is trying to say.
Answer: Yes, we have changed it. The perspective of balancing efficacy and cardiotoxicity were heightened interest in 12-month and 6-month of durations of trastuzumab treatments.
Discussion (p17), comment:
“This benefit-risk analysis is important information to help clinicians and patients choose optimum duration”
And policy makers? See my earlier comment.
Answer: Yes, we have added it.
Discussion (p18), syntax:
“…for de-escalating duration treatment, without compromise of their efficacy”
Please change to “…for de-escalating duration of treatment, without compromising efficacy”
Answer: Yes, we have changed it.
Discussion (p18), syntax:
“…that de-escalating chemotherapy was candidate for older and stages I HER2-positive breast cancer”
Please fix the wording, e.g.:
“…that de-escalating chemotherapy was a good candidate for older patients and those with stage I HER2-positive breast cancer”
Answer: Yes, we have changed it.

Discussion (p18), typo:
“…another option of for patients with…”
Please remove “of”.

Answer: Yes, we have changed it.

Discussion (p18), typos:
“…the results of system review will fill a pivital…”
Please change to
“…the results of our systematic review will fill a pivotal…”

Answer: Yes, we have changed it.

Page 20:
“Patient and public involvement
No patient involvement”
I advise that you have some patient input – see my earlier comment.

Answer: We changed “Patient and public involvement” to “Patient consent for publication” according to BMJ Open instructions for authors.

VERSION 2 – REVIEW

REVIEWER	Dr Caroline S Clarke University College London, UK
REVIEW RETURNED	01-Sep-2020

GENERAL COMMENTS	Thanks very much for the opportunity to see this interesting and useful paper again. The changes that the authors have made since last time have been very helpful in clarifying and justifying their work and I think have greatly improved the paper. There are still some typos/language issues, but far fewer than before, so thank you to the authors for also making those improvements. I have not highlighted the remaining typos and minor language issues in my comments here (although they would ideally be fixed, please); I mention here only those where I think the meaning is not clear. Specific comments: Ethics and dissemination (p17), clarity: “that a drop to 83% four-year DFS with six months trastuzumab would be also acceptable” Please explicitly state what this is compared to, and mention that this is a trade-off against cardiotoxicity. Ethics and dissemination (p17), clarity: “The perspective of balancing efficacy and cardiotoxicity were heightened interest in 12-month and 6-month of durations of trastuzumab treatments.” Please clarify this. Do you mean something like, “The requirement to balance efficacy and side effects (i.e. cardiotoxicity) has led to heightened interest in reducing trastuzumab duration from 12 months to 6 months”. Patient and public involvement (p18) I see that you have not had any input from patients and the public so far, and I would advise that you do have some input from these groups while performing and writing up the work, because if patient advocacy groups are not on board with any recommendations that you make, then it will be very unlikely that reductions in treatment duration will become acceptable.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Thanks for your valuable review comments. Our team learns more about network meta-analysis. We believe that we have many more opportunities to invite you to review our manuscript in the future. Please see detailed feedback to your comments as following:

Ethics and dissemination (p17), clarity:
“that a drop to 83% four-year DFS with six months trastuzumab would be also acceptable”. Please explicitly state what this is compared to, and mention that this is a trade-off against cardiotoxicity.
Answer: With the increase in rates of patients reporting 12-month trastuzumab induced cardiotoxicity, most clinicians suggested that a drop to 83% four-year DFS with six months trastuzumab would be also acceptable.

Ethics and dissemination (p17), clarity:

“The perspective of balancing efficacy and cardiotoxicity were heightened interest in 12-month and 6-month of durations of trastuzumab treatments.” Please clarify this. Do you mean something like, “The requirement to balance efficacy and side effects (i.e. cardiotoxicity) has led to heightened interest in reducing trastuzumab duration from 12 months to 6 months”.
Answer: Yes, we have revised it. The requirement to balance efficacy and side effects (i.e. cardiotoxicity) has led to raise interest in reducing trastuzumab duration from 12 months to six months.

Patient and public involvement (p18)
I see that you have not had any input from patients and the public so far, and I would advise that you do have some input from these groups while performing and writing up the work, because if patient advocacy groups are not on board with any recommendations that you make, then it will be very unlikely that reductions in treatment duration will become acceptable.
Answer: Yes, we added it in main manuscript text.
Patient and public involvement
The manuscript was developed without patient or public participation. Breast cancer patient organizations will participate in the discussion and dissemination of research results. A summary of the findings will be provided to the Chinese society of clinical oncology (CSCO).